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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/752,231	12/29/2000	Abraham Grossman	Q01/006	4570

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/752,231	GROSSMAN, ABRAHAM	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed April 19, 2004. Currently, claims 1-13 are pending.

2. All arguments have been thoroughly reviewed. Upon reconsideration and consideration of the amendments, the examiner determined, that the previous rejections did not thoroughly address the limitations "on the basis of the affinity of said replicatable RNA template to the target" are required by the instant claims.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Priority

4. This application claims priority to PCT/US99/15030, filed July 1, 1999 and provisional application 60/091,578, filed July 2, 1998.

Drawings

5. The drawings are objected to. Figure 1 contains a sequence which is not identified by SEQ ID NO: in either the brief description of the drawings or on the figure itself. Appropriate correction is required. The sequence appears as though it may be SEQ ID NO: 1.

Response to amendments to the specification. The Brief Description of Drawings is not found on page 7. The brief description of drawings is found on page 8. Appropriate correction is required prior to allowance.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-3, 6-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Short (US Publication 2002/0006620, January 17, 2002).

Short teaches a method for identifying one or more complexes from a library of complexes where the complex or complexes are selected for their ability to perform a preselected or desired function on a target molecule or by having a preselected structure (abstract). Short teaches that repeated cycles of selection for the highest affinity and error-prone PCR can lead to increased diversity and oligomers with an even greater affinity. Short specifically teaches that a library of morphatides is prepared, screening the library of morphatides of the first step by contacting, binding, or associating the morphatides with one or more suitable target molecules upon which a morphatide performs a preselected or desired function or to which a morphatide binds or associates and separating the morphatides performing the binding or associating through the preselected structure from the library of morphatides and target molecules,

thereby identifying one or more complexes from a library (para 21). Short teaches a method where the scaffolding molecules is a nucleic acid molecules, the molecule is amplified utilizing a process known as sloppy PCR, error-prone PCR or mutagenic PCR (para 38). Error-prone, or sloppy or mutagenic PCR is a process for performing the PCR under conditions where the copying fidelity of the DNA polymerase is low, such that a high rate of point mutations is obtained along the entire length of the PCR product (para 38). This library is then screened to enrich or select for any desired interaction (typically a binding event) with any target (substrate or substrates) of interest (para 38)(limitations of Claim 1). As seen in Figure 1, aptamer selection is added to a receptor, allowed to bind and eluted. As seen in Figure 2, the template is amplified using error-prone or sloppy amplification. A morphatide is created and selected for binding morphatide. Figure 3B illustrates a library, followed with coupling, capturing, elution and PCR mutate to perform the iterative procedure. Short teaches that either DNA or RNA molecules may be used as scaffolding molecules (limitations of Claim 3). Short teaches that screening of and selection from shape and structure libraries represents an approach to generating complexes of molecules that recognize and bind target molecules (para 54). Short teaches that the separation step may be performed by either separating the morphatides which do not perform the preselected or desired function or which do not bind or associated or alternatively by separating the morphatides which bind or associate through a preselected structure (para 85)(limitations of Claim 6). Short teaches that separating may be through centrifugation; electrophoresis; biopanning; solubility differences; chromatography;

fluorescence sorting, properties such as physical, chemical or electrical; photochemical; magnetic; and visible detection (para 86)(limitations of Claim 2, 7). Short teaches that the target molecule is bound to a solid support (para 87). Example 9 describes in detail the general methodology for the generation and screening of morphatides (para 179-214). Example 9 teaches repeating the amplification, immobilization, screening method (para 189)(limitations of Claim 8-9). Short teaches that the pool is used for selection of target molecules coupled to magnetic beads and the supernatants from the washing steps are collected in a tube.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 4-5, 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Short (US Publication 2002/0006620, January 17, 2002) in view of Rohde et al. (J. Mol. Biol. Vol. 249, pages 754-762, 1995).

Short teaches a method for identifying one or more complexes from a library of complexes where the complex or complexes are selected for their ability to perform a preselected or desired function on a target molecule or by having a preselected structure (abstract). Short teaches that repeated cycles of selection for the highest affinity and error-prone PCR can lead to increased diversity and oligomers with an even

greater affinity. Short specifically teaches that a library of morphatides is prepared, screening the library of morphatides of the first step by contacting, binding, or associating the morphatides with one or more suitable target molecules upon which a morphatide performs a preselected or desired function or to which a morphatide binds or associates and separating the morphatides performing the binding or associating through the preselected structure from the library of morphatides and target molecules, thereby identifying one or more complexes from a library (para 21). Short teaches a method where the scaffolding molecules is a nucleic acid molecules, the molecule is amplified utilizing a process known as sloppy PCR, error-prone PCR or mutagenic PCR (para 38). Error-prone, or sloppy or mutagenic PCR is a process for performing the PCR under conditions where the copying fidelity of the DNA polymerase is low, such that a high rate of point mutations is obtained along the entire length of the PCR product (para 38). This library is then screened to enrich or select for any desired interaction (typically a binding event) with any target (substrate or substrates) of interest (para 38)(limitations of Claim 1). As seen in Figure 1, aptamer selection is added to a receptor, allowed to bind and eluted. As seen in Figure 2, the template is amplified using error-prone or sloppy amplification. A morphatide is created and selected for binding morphatide. Figure 3B illustrates a library, followed with coupling, capturing, elution and PCR mutate to perform the iterative procedure. Short teaches that either DNA or RNA molecules may be used as scaffolding molecules (limitations of Claim 3). Short teaches that screening of and selection from shape and structure libraries represents an approach to generating complexes of molecules that recognize and bind

target molecules (para 54). Short teaches that the separation step may be performed by either separating the morphatides which do not perform the preselected or desired function or which do not bind or associated or alternatively by separating the morphatides which bind or associate through a preselected structure (para 85)(limitations of Claim 6). Short teaches that separating may be through centrifugation; electrophoresis; biopanning; solubility differences; chromatography; fluorescence sorting, properties such as physical, chemical or electrical; photochemical; magnetic; and visible detection (para 86)(limitations of Claim 2, 7). Short teaches that the target molecule is bound to a solid support (para 87). Example 9 describes in detail the general methodology for the generation and screening of morphatides (para 179-214). Example 9 teaches repeating the amplification, immobilization, screening method (para 189)(limitations of Claim 8-9). Short teaches that the pool is used for selection of target molecules coupled to magnetic beads and the supernatants from the washing steps are collected in a tube.

Short does not specifically teach using QB replicase to introduce errors into the replicatable RNA.

Rohde et al. (herein referred to as Rhode) teaches that QB replicase is prone to error and mutant incorporation. Sequences of several cDNA clones were amplified by QB replicase and a surprisingly broad mutant distribution was found (abstract). Rohde teaches that the consensus sequence never made up more than 40% of the total population and was accompanied by many mutants (abstract). Most mutants had several base exchanges, insertions and/or deletions: up to nine of the total 86

nucleotides were changed. Rohde teaches that QB functions as an error-prone replicase for RNA.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the selection method of Short to include the RNA polymerase QB, as taught by Rohde. Rohde specifically teaches that QB generates a very broad mutant distribution which includes mutants that have several base exchanges, insertions, and/or deletions. The method of Short relies upon error-prone amplification or sloppy PCR. The ordinary artisan would have been motivated to have incorporated the QB RNA polymerase into the method of Short because QB provides a very broad mutant distribution which is essential to the selection method of Short. Short suggests that any random or directed mutagenesis technique would allow for modification of the replicatable RNA and enable screening. The art is clear that using QB replicase is a random technique which generates mutants upon replication. Thus, modifying the method of Short for selecting molecules with affinity to a target with the use of the random method of replication using QB replicase would have been obvious at the time the invention was made.

Conclusion

8. No claims allowable over the art.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Gold et al. (US Pat. 5,270,163, December 1993) teaches a method for identifying nucleic acids ligands.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
July 11, 2004